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| EXAMINER | |
|---|---|
| PRIEBE, SCOTT DAVID | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/717,845 | GJERSET ET AL. | |
| | Examiner | Art Unit | |
| | Scott D. Priebe, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Claim Objections*

Claims 15, 18, 25, 32 are objected to because of the following informalities. In claim 15, "activity" should be --activities--. These two proteins do not have the same tumor suppressor activity. In claims 18, 25, and 32, "delivery vehicle" is singular, so "liposomes, polylysine carrier complexes" should be --a liposome, a polylysine carrier complex--. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

Claims 15-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15-35 introduce new matter into the application. Claim 15 recites "coding sequences encoding polypeptides having p53 and p14ARF tumor suppressor activities." The polypeptides are only required to have the tumor suppressor activities of p53 and p14ARF, and thus need not have any structural relationship to p53 and p14ARF. Applicant indicates that this

limitation of the bicistronic construct is supported in the original specification at page 4, lines 2-5, and in the original claims.

However, page 4, lines 2-5, of the specification recites: "a bicistronic construct of p53 and p14ARF genes (or gene variants thereof), which express protein having tumor suppressor activity" (emphasis added), and similarly original claim 1 recites: "bicistronic construct comprising p53 and p14ARF genes or gene variants thereof" (emphasis added), and claim 7 required that the gene variants encode proteins with tumor suppressor activity. The bicistronic construct originally disclosed was directed to p53 and p14ARF genes or gene variants thereof (i.e. homologs of p53 and p14ARF genes), not to some structurally undefined coding sequences that encoded polypeptides with the same tumor suppressor activities of p53 and p14ARF, as now being claimed. Thus, the instant claims are directed to a bicistronic construct that is broader than that originally disclosed, because the claims embrace constructs with coding sequences for polypeptides that have the activity of p53 and/or p14ARF, but not necessarily structural relationship to p53 and/or p14ARF or their respective genes, i.e. the coding sequences do not have to be gene variants of the p53 and/or p14ARF genes.

To the extent that the bicistronic construct of the instant claims embraces the bicistronic construct previously claimed, i.e. "bicistronic construct comprising p53 and p14ARF genes or gene variants thereof," the specification fails to provide an adequate written description of "gene variants" of the p53 and p14ARF genes. The only description of "gene variants" for either p53 or p14ARF states that they are "variants of p53 or p14ARF (such as mutated or truncated forms of these tumor suppressors) that retain the tumor suppressor activity of the protein, or that display enhanced tumor suppressor activity" (page 6, lines 26-29). The specification does not provide

any structural information regarding such "gene variants" whose products retain tumor suppressor activity, much less that display enhanced tumor suppressor activity, nor is there evidence of record that such variants or their structure were well known in the prior art.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. Unlike the situations reviewed by the courts and the Board, the instant specification does not even describe how one might isolate or make the recited "gene variants". Consequently, the specification does not provide an adequate written description of

"gene variants" of p53 and p14ARF genes to allow one of skill in the art to recognize that Applicant was in possession of the "gene variants" required by the claimed invention.

Applicant's arguments filed 1/30/06 have been fully considered but they are not persuasive. Applicant argues only that the cancellation of claims 1-14 renders the previous rejection moot, without explaining how the new claim limitations would obviate similar grounds of rejection.

***Claim Rejections - 35 USC § 102***

Claims 15, 17-22, 24-26, 28, 29, 31-33, and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Depinho, R.A., US 2002/0193325, as evidenced by Tango et al., Hum. Gene Ther. 13 :1373-1382, 2002.

Depinho discloses an expression vector comprising nucleic acids encoding p19ARF and p53, pharmaceutical compositions comprising the vector, and methods for treating tumor cells *in vitro* or cancer in patients with the vector. Expression of both proteins in a tumor cell leads to growth arrest and apoptosis. The vector can be a naked DNA vector or viral vector based upon HSV, adenovirus, or AAV, or can be delivered to tumor cells in a liposomal formulation. Cancers that can be treated include melanoma, bladder carcinoma, oral carcinoma,, lung carcinoma, and lymphoid neoplasms such as B-cell chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphomas. p19ARF is the murine homolog of p14ARF (Tango et al., Hum. Gene Ther. 13 :1373-1382, 2002, at page 1373 col. 2), i.e. it has the tumor suppressor activity of p14ARF. See Fig. 11A, paragraphs 0031-0035, 0037-0040, 0081, claims 4 and 10.

Applicant's arguments filed 1/30/06 have been fully considered but they are not persuasive. Applicant argues only that the cancellation of claims 1-12 and 14 renders the previous rejection moot, without explaining how the new claim limitations would obviate similar grounds of rejection.

Claims 15-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al., US 5,747,469 in view of either or both of Lu et al. (Cancer Res. 62: 1305-1310, 01 March 2002) or Tango et al. (Hum. Gene Ther. 13: 1373-1382, 20 July 2002) further in view of Almond et al., WO 99/47690.

Roth describes viral vectors, such as retrovirus, adenovirus, AAV, HSV, or CMV vectors, or non-viral vectors in liposomal formulations, that express p53, and methods of treating tumors or cancer in an individual, such as skin, lung, and breast cancer by administration of the vector to tumors and also treating the patient with chemotherapy or radiation therapy. See entire document, especially the claims. Roth does not teach including a p14ARF gene on the vector, i.e. a bicistronic construct or vector.

However, Lu disclosed that tumors without a p53 mutation are often resistant to p53 gene therapy (page 1305). Lu disclosed that a major factor in the resistance to p53 gene therapy involving p53+ tumor cells is likely to be loss of ARF expression in the p53+ tumor cells and the resultant inhibition and increased degradation of p53 mediated by MDM2, whose expression is induced by p53, and which is inhibited by ARF (page 1307, col. 2). Lu showed that co-transfection with separate vectors encoding p14ARF and p53 was significantly more effective at inducing cell death in tumor cell lines (page 1306). Lu taught that co-expression of p53 with

ARF in gene therapy will be more effective for tumors that have p53+ tumor cells (page 1309, col. 1).

Also, Tango disclosed that co-transfection of tumor cells both *in vitro* and *in vivo* with vectors (administered simultaneously) expressing p14ARF (the human homolog of the mouse p19ARF) and p53 greatly enhances the tumoricidal effect of either p53 or ARF gene therapy alone as ectopic expression of ARF enhances the effectiveness of p53 gene therapy. Like Lu, Tango taught that ARF inhibits MDM2, which then reduces or eliminates increased degradation of p53. See entire document, especially pages 1380-1381.

Neither Lu nor Tango suggests including both the p53 and p14ARF genes on a bicistronic construct or vector.

However, Almond et al. generally describes the treatment of cancer with two or more genes at the same time, which augments the action of one or both genes. It teaches that the use of separate vectors, each encoding a different therapeutic gene, presents a variety of problems including immunogenicity, oncogenicity, and reduced transduction efficiency (page 3). Almond discloses that these problems can be reduced by introducing both therapeutic genes, e.g. including a p53 gene, on a single vector, such as an adenovirus, AAV, herpesvirus, or retrovirus vector or in a liposome, which ensures that both genes are expressed in the same cells. The genes may either be present in the vector in separate expression cassettes, i.e. each under control of a different promoter, or they can be present in a single expression cassette under control of the same promoter with an IRES separating the genes. (See pages 4-10, 84 for overview). Almond also teaches that the multi-gene therapy can be combined with radiation therapy or chemotherapy (page 91).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a p14ARF gene on the vector of Roth, either under control of the same promoter as the p53 gene with an IRES between the p53 and ARF genes, or under control of a different promoter than that of the p53 gene. (Either arrangement meets the limitation of a bicistronic construct). One would have been motivated to include the p14ARF gene because Lu and Tango taught that co-expression of p14ARF with p53 improved the effectiveness of the p53 by blocking the inhibitory effects of MDM2 on p53. Both taught that the combination would be more effective than p53 gene therapy alone. From the teachings of Almond, one would have been motivated to include both the p53 and p14ARF genes on the same vector to avoid the problems associated with using separate vectors in gene therapy, and to improve the efficiency of the gene therapy.

Applicant's arguments filed 1/30/06 have been fully considered but they are not persuasive. Applicant argues that the invention produces results that would be unexpected from the combination of prior art cited in the rejection: the bicistronic construct was effective at a dose 20 times lower than with a construct expressing p53 or p14ARF alone (page 8, lines 6-10); the bicistronic vector was more effective than a combination of two single gene vectors (page 8, lines 10-12); the viability of several tumor cell lines of different origins was abolished with low vector to cell rations (page 8, lines 21-22); and that the bicistronic vector was effective at a dose of a vector expressing p53 alone that required chemotherapy to be effective (page 9, lines 1-16).

In response, the prior art cited (Lu and Tango) disclosed that recombinant expression of the combination of p53 and p14ARF was significantly more effective than expression of either alone, particularly on cancer cells that had endogenous p53 activity, and that inclusion of two

genes on a single vector would be more effective and require a lower total vector dose than a combination of two vectors each comprising one of the two genes (Almond). Thus, results of these types would not have been unexpected. In addition, the unexpected results to which Applicant refers were obtained in the context of a single specific use of the bicistronic construct, transfection of cultured DLD-1 or N202 cell lines (not primary cancer cells) with adenoviral vectors. Claims 15-21 are directed to the construct itself, not to any particular method of using it, and claims 22-35 are not limited to treating cancer cell lines DLD-1 and N202 in culture, but embrace treatment of any malignant of metastatic cancer cells in whatever milieu they might be found, e.g. in culture or *in vivo*.

***Double Patenting***

Applicant is advised that should claims 22-28 be found allowable, claims 29-35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The only difference between these claims is the effects, recited in the preamble, resulting from carrying out the method steps, inducing killing or apoptosis in claim 22 or inducing growth arrest in claim 29. However, both outcomes would be achieved by practicing the method steps recited in both sets of claims regardless of the cancer cell population being treated, i.e. some of the treated cancer cells will undergo growth arrest, and some of these will subsequently undergo apoptosis. See instant Fig. 1, for example.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

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Art Unit 1633